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(54) PHARMACEUTICAL COMPOSITION

(71) We, DEUTSCHE LAEVOSAN-GESELLSCHAFT C.F. BOEHRINGER & SOHNE G.M.B.H. & CO., KG., of Mannheim, Germany, a German Kommaditgesellschaft, and SUDDEUTSCHE ZUCKER - AKTIENGESELLSCHAFT, of 10, Maximilian-Strasse, Mannheim, Germany, a Body Corporate organised under the laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with a pharmaceutical composition for the treatment and prophylaxis of hepatopathias, dyspepsias, dyaboises and nutritional disturbances of unweaned infants, as well as phenomena resulting therefrom.

Hepatopathias, especially chronic hepatopathias and, in particular, hepatic encephalopathias, are diseases which have hitherto not been satisfactorily susceptible to medicinal therapy. In many cases, the known pharmaceuticals were ineffective and, furthermore, the use of some of them involved certain risks because of their not inconsiderable toxicity. It has already been found that lactulose has a favourable action against such diseases but, nevertheless, this produces certain undesirable side effects.

Therefore, it is an object of the present invention to overcome these disadvantages.

The pharmaceutical composition according to the present invention for the treatment and prophylaxis of hepatopathias and nutritional disturbances of unweaned infants, comprises at least one of the following substances:

a) a saccharide of the general formula:—

$$(gal)_n\text{-saccharose},$$

in which gal is a galactose residue and n is an integer
b) an oligofructosan;
c) a polyfructosan;
d) a kestose,

in admixture with a solid or liquid pharmaceutical carrier or diluent and with a flavouring agent and/or colouring material.

The pharmaceutical composition according to the present invention preferably contains raffinose and/or insulin as the active substance. Further examples of sugars of the above-mentioned groups which can also be used include 1-kestose, 6-kestose and neokestose.

The pharmaceutical compositions according to the present invention possess, surprisingly, an outstanding pharmacological effectiveness. This effectiveness consists in a healing and prophylactic action in the case of hepatopathias, especially chronic hepatopathios and, in particular, hepatic encephthalopathias, dyspepsias, dysbioses, as well as nutritional disturbances in unweaned infants, infantile dyspepsias and the like, as well as their resultant phenomena. Especially good results have been obtained in clinical investigation in the case of chronic coma hepaticum, in the case of alcoholic liver cirrhosis and in the case of hepatic encephalopathy.

The actual mode of action of the pharmaceutical composition according to the present invention is not known exactly. However, a common characteristic of the active materials contained in the pharmaceutical compositions according to the present invention is that they reach the colon without having been split and can there be broken down by microorganisms. Since the active materials in question are saccharides with β-fructosidic components and, in some cases, are β-fructofuranose derivatives, then a breakdown must take place by microbial β-fructosidase which, in the case of, for example raffinose, results in the formation of fructose and melibiose. By the further decomposition of these products, there are probably formed organic acids, especially lactic acid, which result in an observed reduction of the pH value of the colon. The lowering of the pH value in turn leads to an inhibition of the activity of the flora responsible for the formation of

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toxic proteinaceous decomposition products. These toxic proteinaceous decomposition products, such as ammonia and phenolic bodies and the like, have, for their part, a considerable participation in the appearance of the diseases which can be combatted and prevented by the pharmaceutical composition according to the present invention.

In the case of suckling infants, still another mode of action comes into consideration since these exhibit an inherent microbial α-galactosidase (Bifidus type IV) activity so that here, besides the above-mentioned decomposition to fructose and melibiose, there also occurs a decomposition to saccharose and galactose (Bifidus 4-flora).

The pharmaceutical composition according to the present invention is especially suitable for oral or rectal administration and can be administered in any formulation suitable for the selected route. Examples of forms of administration which can be used include powders, soluble powders, crystalline materials, granulates, tablets, for example effervescent tablets, capsules, dragees, syrups, pastes and gums.

If desired, the active materials to be used according to the present invention can be admixed with other therapeutically active agents, for example, with antibiotics, sulphonamides and vitamins. Furthermore, in the case of unchanged indications of the patient, they can also be worked up to or contained in foodstuffs, especially dietetic foodstuffs and foodstuffs for sucklings and children.

Since the active substances of the pharmaceutical compositions according to the present invention are, in reasonable doses, non-toxic, the dosages administered can be determined almost as desired, depending on the particular requirements of the patient. In actual fact, there are normally used daily dosages of between 20 and 250 g., spread out in small amounts over the course of the day. The upper limit of the amount administered is normally determined by a slight laxative effect which occurs when the dosage administered is too high but the effective threshold is an individual characteristic which can easily be ascertained.

The pharmaceutical composition according to the present invention provides considerable advantages in comparison with the previously known pharmaceutical compositions of the same effectiveness. Thus, in comparison with the disaccharide lactulose, there is the advantage that the active materials of the pharmaceutical compositions according to the present invention (tri- and polysaccharides) are much less sweet and, therefore, are less objectionable to patients especially in cases where prolonged administration is indicated. It is also to be borne in mind that lactulose exerts an osmotic action in the intestinal tract which can manifest itself in anything from a slight laxative action to a marked diarrhoea: however, actions of this nature are much less marked in the case of the use of the active materials in the pharmaceutical compositions according to the present invention.

Furthermore, the active materials in the pharmaceutical compositions according to the present invention are not reducing sugars, as is lactulose, they are not hygroscopic, they are less sensitive to alkalis than lactulose (no yellow coloration), they can be readily crystallised and can easily be obtained in a pure state. Furthermore, the active materials used according to the present invention are naturally-occurring materials, whereas lactulose is not.

In comparison with other pharmaceuticals with corresponding effectiveness, especially neomycin, we have found that the pharmaceutical composition according to the present invention is also effective in those cases in which neomycin is ineffective. Furthermore, the active materials used according to the present invention have a considerably lower toxicity and less side effects than has, for example, neomycin, the use of which involves not inconsiderable risks.

The following Examples are given for the purpose of illustrating the present invention:—

Example 1.

Use of raffinose in clinical coma therapy.

A 64 year old patient with chronic coma hepaticum due to alcoholic liver cirrhosis was given 150 g. raffinose daily *per os*, in the form of an aqueous solution. With a constant diet (40 g. protein daily), an initially good response was observed. The coma could be overcome in a way which was just as good as with neomycin therapy. Without the therapy, a relapse occurred which could, however, still be controlled again by raffinose. EEG-observations confirmed the clinical course of the treatment.

The clinical investigation showed that raffinose possesses a favourable action in the case of porto-systemic encephalopathy.

Example 2.

An elderly hospitalised patient with non-characteristic abdominal pains was given barium sulphate for 3 days. On the fourth day, an X-ray was taken of the empty abdomen from a rear posture, whereafter 20 g. raffinose were administered in the form of an aqueous solution. Thereafter, the same amounts of raffinose were administered every 30 30 minutes for a total period of 180 minutes. The calculation of the colonic volume from the X-rays gave a maximum volume increase of 400 ml.

Example 3.

Reduction of the ammonia level in rats with a porto-caval shunt.

After application of a porto-caval shunt,

rats showed a hyperamonaemia which, in the course of time, increased from a normal value of about 100 μg./100 ml. to 600 μg./100 ml.

For the treatment, 0.6 g. raffinose, in the form of an aqueous solution, was adminstered to the animals three times daily for 48 hours by means of a stomach probe. An identical amount of lactulose and of saccharose was administered to two control groups. The amonmia level was determined before and after the experiments. The results obtained are set out graphically in the accompanying drawing. They clearly show the superiority of the action of the raffinose in comparison with the also favourable action of lactulose, whereas, in the case of saccharose, a negative effect occurred. This means that the ammonia level sinks the most markedly in the case of the adminstration of raffinose.

Example 4.
Effectiveness of inulin in hepatic encephalopathy.

In a clinical investigation, inulin was administered, in the form of an aqueous solution, to a patient with hepatic encephalopathy at a dosage rate which increased from 50 to 200 g. per day. A marked improvement of the condition of the patient was observed. Whereas before the treatment, the writing test and match-stick test were negative, after administration of the inulin, the clearly positive reaction occurred in both cases. At the same time, the ammonia level in the blood dropped.

Example 5.
Rectal administration.

A 47 year old male patient with hepatic coma, stage III, was given a total of 1000 ml. of a 15% aqueous solution of raffinose, the pH of which was buffered, divided into three doses over the course of the day, administration at a rapid rate being by means of a balloon catheter. After the treatment had been carried out, there was observed an improvement of consciousness, an improvement of the EEG, and a reduction of the venous and arterial ammonia level. Further treatment was by the oral administration of raffinose.

Example 6.

Adminstration of raffinose in doses of 20—150 g. daily, especially of 40—60 g. and advantageously of 46 g., raffinose in 4 tablets (4 individual doses) spread out over the day. A single dose corresponds to 11.5 g. rafinose.

Formulation of the tablets.

11.5 g raffinose
0.523 g. polyglycol (M.W. 1500)
0.0125 g. lemon flavouring
0.1575 g. citric acid
0.5 g. talc

Example 7.
Formulation of a raffinose granulate.

100 g. raffinose are granulated with a 10% starch paste and coloured with 0.2 mg.% (i.e. 0.2 mg. per 100 g. granulate mass) tartrazine yellow.

WHAT WE CLAIM IS:—

1. Pharmaceutical composition for the treatment and prophylaxis of hepatopathias and nutrional disturbance of unweaned infants, comprising at least one of the following substances:

a) a saccharide of the general formula:—

$(gal)_n$-saccharose

in which gal is a galactose residue and n is an integer;

b) an oligofructosan;
c) a polyfructosan;
d) a kestose,

in admixture with a solid or liquid pharmaceutical carrier or diluent and with a flavouring agent and/or colouring material.

2. Pharmaceutical composition according to claim 1, wherein the saccharide of the given general formula is raffinose.

3. Pharmaceutical composition according to claim 1 or 2, wherein the fructosan is inulin.

4. Pharmaceutical composition according to any of the preceding claims, wherein at least one antibiotic and/or sulphonamide and/or vitamin is present.

5. Pharmaceutical composition according to any of the preceding claims, whenever in the form of a powder, crystalline material, tablet, granulate, capsule, dragee, syrup, paste or gum.

6. Pharmaceutical composition according to claim 1, substantially as hereinbefore described and exemplified.

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1305071 COMPLETE SPECIFICATION
1 SHEET *This drawing is a reproduction of the Original on a reduced scale*